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Dear Joshua / Dr. Lederberg,

I often treat these alternatives as you addressed me by my surname, but signed off with your first name, and this — if one can trust the evidence gathered on lower primates — is bound to drive me to neurasthenia, subliminal Oedipus complex, hydrophobia, or whatever other purely psychologic ills dogs may exhibit. At any rate, it establishes an atmosphere of ambivalence and uncertainty — just the thing for talking about incomplete forms of virus.

When you equate incompleteness with an imperfect viral wall, the available direct evidence is all on your side: these forms are more fragile on drying (Schlesinger), have variable lipid content (Uhler + Gard) and less carbohydrate (Schäfer) — the latter two are certainly both on the outside of the particle. The fragility, I think, is sufficient to account for the lower RNA content, as this is tested invariably after rough preparative manhandling. The beauty of your hypothesis is that it automatically covers some of the things nobody dares (= incomplete virus) mention in public, viz., that "IV-subscript chorion" is not necessarily IV_{amnion}, and $IV_{mouse\ brain}$ is certainly not $IV_{ale.}$ or $IV_{amn.}$. If the case of penetration

comes in as the limiting parameter, this is just what one should expect. Also, the pious hope may be entertained that we — I mean you — may find some way of oiling the passage through the exoplasm or, alternatively, put some sort of artificial exo-skeleton on IV and make it deliver the goods inside the cell. There is only one observation I can think of that doesn't fall in line: IV is quantitatively as good an interfering agent as is infective virus. In interference expts, of course, both are used after heat, UV or CH_2O inactivation, but this still demands an extra assumption, either that interference is not at the reproductive but at the assembly level, or that after inactivation there is no difference between what was formerly infective or non-infective virus. This point should not be taken too seriously: so little is known about the mechanism of interference that to talk of levels is pure presumption.

When you say that the receptor substance may be a natural addition to the emerging virus surface, I am with you; but that this should lengthen the first cycle is just the opposite of what I would deduce. You can pre-incubate virus in vitro, so that its enzyme will destroy all that is destructible, or you can treat it with RDE, and the average first cycle will be just as long as before. In fact, if destruction of the adhering RS would be a prerequisite of reproduction, the second and subsequent cycles

should be longer than the first. From the little evidence there is it looks as if there would be a variable delay after the virus has disappeared from the cell surface but before the earliest next sign (appearance of intracellular CF-antigen) is detectable. From then on there is no difference between first and later cycles. This delay can be overcome by multiple infection of the cells. Cairns thinks that there are good and bad spots on the cell which handicap to varying extent the original infective particles, but have no effect in later cycles. I still think in terms of some cofactor which is statistically distributed in dormant (in vitro) virus preparations, but that all newly formed, nascent particles have enough of it ("the idea is plagiarised from the T2/tryptophane system). Whatever the explanation, I think a difference in extracellular behaviour — as you would have to postulate — runs counter to the evidence.

As regards the work on the stability of viruses, there has been little of it and that at the lowest pedestrian level. Stanley's people have done some during the war, and he got the Nobel Prize in spite of that particular effort. The general agreement on the need of "protective colloids" is a remnant of the heroic era, and is handed down as an article of faith. I believe in it of course, but then I am probably easy prey to superstition. I think the trouble was that

nobody had any sensible idea on how such protection could work in the case of a virus, i.e. who is protecting what. Your formulation of the problem is the first intelligent question asked in this field, and I hope you will have the time to get out the answer. If you are planning to use the bit technique, please let me know and I will send you the necessary gear, as it might take some time to have it made up in Melbourne.

My plans have, unfortunately, changed in the meantime: I will not have to go to Melbourne, as my former collaborator is coming here for a month to finish up the work. This means that I can only hope to hear from you by letter, and perhaps see you again on your way back, if you can afford to stop over in Canberra for a short time.

Yours sincerely

Stephen Fazekas.

I see I haven't answered one of your questions. The expts on the need for allant. fluid in the production of infective virus were all done on hfft, which seemed the obvious choice for this work. We did the main expts in empty eggs (they behave exactly like bits, but one can use larger volumes of fluid), and did the titrations in bits. Here, again, is a first-cycle type behaviour — the average infective output of later cycles is the same whether synthetic medium or allantoic fluid is used as medium in either empty eggs or bits.